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PARKIN, J EXAMINER

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FINNEGAN, HENDERSON, FARABOW,
GARRETT AND DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005-3315

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DATE MAILED: 10/18/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 7/11/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 15-16, 18-20, & 28-31 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-14, 17, 21-28, 32-36 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 15-16, 18-20, & 28-31 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Detailed Office Action

15. Acknowledgement is hereby made of Paper no. 21 (filed July 11, 1995) in which the applicants request examination after final rejection under 37 C.F.R. § 1.129(a). Claims 15, 16, 18-20, and 29-31 are currently pending in the instant application. The applicants are reminded that claims 17, 21-28, and 32-36 were cancelled on page 2 of Paper no. 14 (filed October 11, 1994), without prejudice, to advance prosecution of the case.

16. Claims 29-31, directed towards immunological complexes comprising isolated and purified HIV-1 proteins (e.g. p12 and p18) and antibody directed against said proteins, were previously rejected under 35 U.S.C. § 101 because the claimed invention lacked patentable utility. The previous examiner noted in the Advisory Action (Paper no. 16) dated November 11, 1994, that

> Applicant argues that immune complexes have utility as chemical intermediates for purifying members of the immune complexes. This is not deemed to be persuasive because the disclosed utility is directed to detecting the presence of anti-HIV antibodies, not purifying immune complex components. The claimed complexes have no utility of themselves in the instant specification. The only context of the complexes in the instant invention is as a final product in the method of detecting the presence of antibodies or antigens.

It was argued by the applicants in Paper no. 23 (filed July 11, 1995) on page 4 that "In this case, as shown above and set forth in the Amendment and Exhibits filed October 11, 1994 (see pages 4-7 and Exhibits 1-2), one of ordinary skill in the art would readily see the utility of the claimed invention of claims 29-31." Specific examples were disclosed from the

original specification on pages 4 (lines 1-5), 10 (lines 21-25), and 26 (lines 15-21). However, it should be noted that pages 4 and 26 of the specification are silent with respect to any written description of the recited immune complexes. Page 10 describes the analysis of immune complexes by SDS-PAGE. It was reported by applicants that "The main protein (p25) detected after purification of ^{35}S-methionine labeled virus has a molecular weight of about 25,000 (or 25K). This is the only protein detectable under such labelling conditions which is recognized by the serum of patient 1. By analogy with other retroviruses, this major protein was considered to be located in the viral core."

The specification does not contain a written description of immune complexes involving either the p12 or p18 proteins and an antibody directed against said proteins. However, a *prima facie* showing of no utility under 35 U.S.C. § 101 must contain the following elements:

> i) a well-reasoned statement that clearly sets forth the reasoning used in concluding that the asserted utility is not credible;
> ii) support for factual findings relied upon in reaching this conclusion; and
> iii) support for any conclusions regarding evidence provided by the applicant in support of an asserted utility.

Although the applicants do not disclose a specific utility for the claimed viral antigen-antibody immune complexes, said complexes can be employed, *inter alia*, as immunogens to elicit the formation of highly specific antiserum (see Higgins, P., 1980 Experientia 36:889-890). Accordingly, the previous rejection of claims 29-31 under 35 U.S.C. § 101 for an alleged lack of utility has been withdrawn.

17. Claims 15, 16, 18-20, and 29-31 were previously rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention (i.e. failing to provide an enabling disclosure). The previous examiner reported the following in the Advisory Action (Paper no. 16) dated November 11, 1994:

> In response to the enablement issue, Applicant has submitted a new catalog of citations from the specification purporting to show support for the claimed invention. A review of the relevant passages is not convincing...Nowhere does the specification teach the isolation and purification of antigens or antibodies from complexes.

It was also noted by the previous Examiner that the specification was silent with respect to the production of monoclonal antibodies.

Applicants argue that reference was made to art-recognized purification techniques in the instant application. Specifically, page 12 of the specification states that "one may use purification procedures such as disclosed by Montelaro et al., J. of Virology, June 1982, pp. 1029-1038." A copy of this reference was enclosed with Paper no. 14, filed October 11, 1994. Montelaro et al. (1982) disclose the large-scale production and purification of four equine infectious anemia virus (EIAV) non-glycosylated virion proteins designated p26, p15, p11, and p9. The virion proteins were solublized in guanidine hydrochloride and resolved on a Sepharose 6B column. Additional purification of the p11 and p9 virion proteins was performed via ion-exchange chromatography on a phosphocellulose column. SDS-PAGE analysis further confirmed the efficient purification of said proteins.

It is the present Examiner's position that one skilled in the art would be capable of employing the purification scheme disclosed by Montelaro et al. (1982) in analogous lentiviral systems. Absent

teachings to the contrary, the skilled artisan would have a reasonable expectation of obtaining similar results with HIV-1 virion proteins employing the disclosed purification schemes. Accordingly, the previous rejection of claims 15, 16, 18-20, and 29-31 under 35 U.S.C. § 112, first paragraph, as set forth in prior Office Actions is untenable and has been withdrawn.

18. Claims 15, 16, and 18-20 were rejected under 35 U.S.C. § 103 as being unpatentable over Barre-Sinoussi et al. (1985, Retroviruses and Human Pathology, Gallo et al., Eds., pp 343-351). Barre-Sinoussi et al. (1985) discloses the identification of four major components of the HIV-1 virion with apparent molecular weights of 45,000, 25,000, 18,000, and 13,000 daltons. Virus was radiolabeled with ^{35}S-methionine, solubilized, and resolved by SDS-PAGE. Radioimmunoprecipitation and Western analysis of the viral proteins was also performed. Applicants traverse this rejection based upon the following grounds:

> i) it has not been shown that the Barre-Sinoussi document was published prior to the filing date of parent application serial no. 06/706,562, filed February 28, 1985; applicants submitted a letter from the publisher that published a full-text article from which this abstract was derived, indicating a publication date of April 08, 1986 for the full-text article (see Paper no. 24);
> ii) the Barre-Sinoussi abstract is not an enabling disclosure (i.e. it does not disclose how to obtain the specified virus) that could support a 35 U.S.C. § 103 rejection of the aforementioned claims; and
> iii) the applicants' foreign priority documents (Great Britain 83/24800 (filed 09-15-93) and South Africa 84/7005 (filed 09-16-84)) purportedly predate the publication date of said reference.

Applicants' arguments recited *supra* have been fully considered but they are not deemed to be persuasive.

Applicants have not demonstrated that the publication date of the abstract was subsequent to the filing date of application serial no. 06/706,562, filed February 28, 1985. The disclosed letter containing the publication date of the full-text article is not directed towards the publication date of the Barre-Sinoussi et al. (1985) abstract. Absent evidence to the contrary from the applicant, the Examiner asserts that the publication date of the abstract precedes the filing date of the application. The data contained in the abstract was presented at the International Symposium on Retroviruses and Human Pathology, held on September 24-26, 1984. Accordingly, one would anticipate that copies of said abstract were available at the meeting or shortly thereafter.

It was further argued by applicants that the recited abstract was non-enabling because it "nowhere states how to obtain the virus from which the proteins are derived." The first sentence of the abstract clearly states that "LAV virus was isolated from patients with AIDS or with lymphadenopathy. The virions contained 4 major protein components (p45, p25, p18, p13)." This piece of art clearly teaches that the specified virus can be obtained from lymphadenopathy or AIDS patients. It was recognized in the art that HIV-1 could be propagated in human lymphoid cultures. Accordingly, one of ordinary skill in the art would have been able to isolate and purify the virus from AIDS, ARC, or lymphadenopathy patients and propagate said virus using standard virologic techniques. The purified virus could readily be utilized to generate immunological reagents to the specified viral proteins.

Finally, the applicants claimed foreign priority to GB 83/24800 and SA 84/7005 filed September 15, 1983 and September 16, 1984, respectively. However, perusal of related US applications reveals that the

specification of 06/558,109 (filed December 05, 1983) is silent with respect to the isolation and purification of the putative viral proteins p12, p15, and p18. The specification specifically states that "The viral origin of other proteins seen in polyacrylamide gel electrophoresis of purified virus is more difficult to assess." Accordingly, domestic or foreign priority, as it pertains to the claimed material, can not be extended any earlier than the filing date of application 06/706,562 (filed February 28, 1985). Therefore, the claim to foreign priority under 35 U.S.C. § 119 is moot.

The previous rejection of claims 15-16 and 18-20 under 35 U.S.C. § 103 as being unpatentable over Barre-Sinoussi et al. (1985) is hereby maintained.

19. The following is a description of 35 U.S.C. § 101 which reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of the this title.

Claims 15-16 and 18-20, drawn towards antibodies which bind with the HIV-1 proteins p12, p15, p18, p25, p36, p42, and p80, are rejected under 35 U.S.C. § 101 because the claimed invention is directed towards non-statutory subject matter.

Claims 15-16 and 18-20, as presently stated, do not sufficiently distinguish over the antibodies as they naturally exist. HIV-1-infected patients invariably generate both humoral and cellular immune responses against the viral structural (i.e. Gag, Pol, and Env), regulatory (Tat, Rev, and Nef), and ancillary (i.e. Vif, Vpr, and Vpu) proteins. One

would anticipate, *a priori*, that said patients will develop a humoral response and produce antibodies to various HIV-1 antigens including the structural (i.e. Gag, Pol, and Env) proteins. These antibodies will appear in the sera of HIV-1-infected patients early during the onset of infection and persist through the clinical sequelae leading to AIDS. Accordingly, the applicants recited antibodies already exist naturally in HIV-1-infected patients. Furthermore, the recited claim language does not specifically identify any non-naturally occurring differences between the claimed antibodies and the structure of said naturally occurring antibodies.

In the absence of directed human intervention, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F. Supp. 68 (1967), 155 U.S.P.Q. 139, (District Court, New Jersey, 1967)).

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Claims 29-31 are directed towards "an immunological complex" comprising a purified HIV-1 protein (e.g. p12 or p18) and an antibody which binds with said protein. However, perusal of the specification indicates that support does not exist for the term "immunological complex" as recited in claims 29-31. The instant application does not contain any recitations of such terminology. Furthermore, the specification is silent pertaining to any indication by the applicant that such complexes were contemplated and considered as an embodiment of the invention. Therefore, the specification fails to provide adequate written support for the claimed invention.

Claims 29-31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 16, 19, 30, and 31, directed towards HIV-1 immunoreactive antibodies and immune complexes, are rejected under 35 U.S.C. 102(a) as being anticipated by McDougal et al. (1985, J. Immunol. Methods 76:171-183). Claim 16 is directed towards an antibody which binds purified HIV-1 p18. Claim 19 recites a mixture of antibodies reactive with HIV-1 p18

and p25. Claim 30 discloses an immunological complex involving HIV-1 p18 and an immunoreactive antibody. Claim 31 merely recites an immune complex containing a protein labeled through art-recognized techniques.

McDougal et al. (1985) discloses an immunoassay for the detection and quantitation of the human immunodeficiency virus (HIV-1_{LAV}). LAV was obtained from J.-C. Chermann (Institut Pasteur, Paris) and propagated in phytohemagglutinin-stimulated lymphoblasts (PHA-blasts). Viral antigens were prepared for Western analysis by ultracentrifugation of LAV-infected culture supernatants over a 30% w/w sucrose cushion. The viral antigens were separated and resolved by SDS-PAGE analysis. Antisera was obtained from a patient with chronic lymphadenopathy syndrome. The IgG fraction was purified by ammonium sulfate precipitation and used for Western analysis. A fraction of purified antisera was also coupled to fluorescein isothiocyanate (FITC).

Figure 1 discloses the immunoreactivity of the IgG antisera with the purified LAV antigens. Antibodies clearly displayed immunoreactivity towards, and bound to (thereby forming an immune complex), a number of LAV antigens including p18, p25, p32, p41, p55, and p65. Additional immunoreactive bands were identified at p12, p15, and p80 (see LAV column, lane 1, above and below the indicated molecular weight markers). Accordingly, the teaching of McDougal et al. (1985) meets the limitations of the aforementioned claims.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the

contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

23. Claims 15-16, 18-20, and 29-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Luciw and Dina (1992, US PAT 5,156,949). Please note the domestic priority claims under 35 U.S.C. 120 dating back to October 31, 1984. Luciw and Dina (1992) disclose the preparation of HIV-1 antigens and antibodies directed against said antigens to be used for diagnostic purposes in the detection of lymphadenopathy syndrome or AIDS. Specifically, the isolation, cloning, and characterization of HIV-1 is described. The expression of HIV polypeptides in prokaryotic and eukaryotic expression systems was disclosed. The prior art also teaches the utilization of these antigenic peptides in ELISA assays to detect anti-HIV-1 antibodies. Detailed purification schemes were provided for the *gag* (e.g. p25 and p16 (a.k.a. p18)) and *env* proteins. The utilization of viral peptides as antigens to produce and obtain anti-HIV antibodies was also taught.

Although this teaching does not specifically disclose the purification of p12 and the generation of antibodies against said protein, it was clearly emphasized that "The gag domain is about 1500 bp and codes for a large precursor protein which is processed to yield proteins of about 25,000 (p25), 16,000 (p16), and 12,000 (p12) daltons. Digestion with SacI and BglII may also be used to obtain exclusively the gag domain with p12, p25, and partial p16 regions." One of ordinary skill in the art

would clearly be capable of expressing the same proteins (p12, p15, p18, p25, p36, p42, and p80) as those claimed by applicants. These antigenic peptides could be utilized to generate high-titer, HIV-1-specific antisera.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was created to utilize the teachings of Luciw and Dina (1992) to generate immunological reagents against HIV-1. These reagents could be employed individually or in combination for diagnostic, therapeutic, and/or obvious commercial purposes.

24. Claims 15-16, 18-20, and 29-31 are rejected under 35 U.S.C. § 103 as being unpatentable over the combined teachings of McDougal et al. (1985, J. Immunol. Methods 76:171-183) and Barre-Sinoussi et al. (1985, Retroviruses Hum. Pathol. Int. Symp. Abstract). The content of the McDougal et al. (1985) teaching is disclosed *supra*. Briefly, methods for propagation and purification of HIV-1_{LAV} were disclosed, methods for the purification of anti-LAV antisera were taught, and antibodies were isolated, purified, and their immunologic properties ascertained. It was reported that these antibodies displayed strong immunoreactivity towards the various purified viral antigens (e.g. p18 and p25) (Figure 1, column LAV, lane 1). Minor immunoreactivity was also displayed towards the viral antigens p12, p15, and p80.

Barre-Sinoussi et al. (1985) disclose the isolation and identification of HIV-1_{LAV} virus from patients with AIDS or lymphadenopathy. It was reported that:

> The virions contained 4 major protein components (p45, p25, p18, p13)...Antibodies against p25 were detected in sera from AIDS and pre-AIDS patients. Indeed, it was the major reacting protein. However, antibodies against p18 and p13 were also detected. Thus, these 3 proteins are considered to be virus-encoded.

This teaching clearly demonstrates that the HIV-1_{LAV} proteins p13 (a.k.a. p12), p18, and p25 are antigenic and immunoreactive.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was created to combine the teachings of McDougal et al. (1985) and Barre-Sinoussi et al. (1985) to generate immunological reagents (i.e. purified viral antigens and immunoreactive antisera) to be used in diagnostic assays of obvious clincial import.

25. Correspondence related to this application may be submitted to Group 1813 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax number for Group 1813 is (703) 305-7939.

26. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D. whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Friday from 8:30 AM to 5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ms. Christine Nucker can be reached at (703) 308-4028. Any inquiry of a general nature or relating to the status of this application

should be directed to the Group 1813 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Group Art Unit 1813

October 12, 1995

ROBERT D. BUDENS
PRIMARY EXAMINER
GROUP 1800